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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Robin M. Silva, Esq.
FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP
Suite 3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,170	CHIRINO ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24 and 27-32* is/are pending in the application.

4a) Of the above claim(s) *24-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Claims

Status of claims

1. Response to restriction requirement filed 05/26/2004 is acknowledged. Applicant elected, without traverse, Group II, claims 24 and 27-32(in part). Claims 23, 25,26 are canceled.

Applicant is requested to amend claims 27-32 to read on the elected invention.

As per election of species, applicant elected sequences that bind to T cell as immunogenic sequences and asparaginyl endopeptidase as cleavage motif. In regard to the latter species, selection of species of a cleavage motif is deemed unnecessary because applicant elected sequences that bind to T cell as immunogenic sequences - note that cleavage motifs are other species of immunogenic sequences; see original claim 14).

Claims 27-31 are withdrawn from consideration as drawn to non-elected species. Claims 24,32 are under examination as drawn to elected species, sequences that bind to T cells.

Claim Rejections - 35 USC § 112, second paragraph.

2. Claims 24, 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is applied for the following reasons:

A. It is not clear what relation the claimed method has to "immunogenicity of target protein" if the beginning step of the method is "inputting backbone structure". A protein backbone is a sequence of (-NH-CH-CO-) moieties stripped of side chains; hence, as a result of this and subsequent method steps, the resulting "variant protein" will not be the related to the originating "target" protein.

B. The claims recite the step of "selecting" (claim 24, step f). The method steps involved in "selecting" are not disclosed in specification, it is not clear what is being encompassed by the step.

C. The language of step a) of claim 24 is not clear: How a structure can be inputted into a computer - does it mean coordinates of the structure (as is being claimed in co-pending 09/903378)?

D. Further, it is not clear how a protein resulting from step c) of claim 24 may not be with an "altered immunogenicity" - al least for the reason that this protein merely "comprises" variant amino acid sequence (meaning that it contains other, non- specified immunogenic moieties). How then the claimed method can be described as "screening" if any resulting protein is expected to have altered immunogenicity?

Note that immunogenicity is broadly described in specification as follows (paragraph #40]:

[0040] By "immunogenicity" herein refers to the ability of a protein to elicit an immune response. **The ability of a protein to elicit an immune response depends on the amino acid sequence or sequences within the protein.** Immunogenicity includes both the humoral and the cellular component of the immune response as outlined below. Amino acid sequences capable of eliciting an immune response are referred to herein as "immunogenic sequences". Preferably immunogenic sequences comprise "MHC binding sites (i.e., MHC binding motifs)", "T cell epitopes" and "B cell epitopes" as outlined below.

Examiner fully agrees that the ability of a protein to elicit an immune response depends on the amino acid sequence or sequences within the protein (highlighted above). Therefore, any product yielded by the method as claimed and having different amino acid content will inevitably have "altered" immunogenicity, and it is not clear how and what is to be selected on the last step of the method to achieve the stated objective of "screening of altered immunogenicity".

E. The language of step b. ii) of claim 24, "removes... by creating" is not clear. Does it mean removes and creates ?

F. Claim 24 is indefinite due to the lack of clarity of the claim language failing to recite a final process step, which agrees back with the preamble. The preamble states that it is "a method of screening", however the last method step recites "selecting of variant with altered immunogenicity". It is not clear how it corresponds to the "screening" objective of the method because, in Examiner's opinion, there is no reason to screen as any of the variant proteins synthesized per step c) will have altered immunogenicity (both because an immunogenic sequence is removed per step b.ii), and because, due to "comprising" language of step c), the final variant protein contains other immunogenic sequences as well.

G. Claim 24: It is not clear whether step b.ii is related to step a) at all, and if yes, whether the design algorithm is applied to the entire protein, or its backbone, or variable positions, or immunogenic sequence

H. Claim 24: Step b) allows substeps I) and ii) to be applied in any order. In both instances, the results are ambiguous and unclear. If step I) is the first, it results in creation of a new primary variant sequence. The specification (paragraph #69) addresses this step in the following very generic way:

[0069]... the methods of the invention involve starting with a target protein and using computational analysis to generate a set of primary sequences. There are a wide variety of computational methods that can be used including sequence alignments of related proteins, structural alignments, structural prediction models, databases, or (preferably) protein design automation computational analysis. Collectively, these computational methods are referred to herein as "computational protein design algorithms". Similarly, libraries of primary variant sequences can be generated via sequence screening using a set of scaffold structures that are created by perturbing the starting structure (using any number of techniques such as molecular dynamics, Monte Carlo analysis) to make changes to the protein (including backbone and side-chain torsion angle changes). Optimal sequences can be selected for each starting structures (or, some set of the top sequences) to make libraries of primary variant sequences.

The resulting, undefined primary variant sequence are not warranted to have the immunogenic sequence to be removed by the next step ii).

If step ii) is the first, would not the then following step I) change the just created "variant immunogenic sequence" ?

I. At claim 24, the term "sequences that bind to T cell epitope" is indefinite because it is a relative term, but no standard of reference has been provided with which to determine whether a particular peptide sequence binds to bind to T cell epitope or not. As there are many types of non-specific interactions - e.g., hydrogen bonds - any amino acid residue is viewed as capable of interacting with another. Accordingly, it is not possible to determine what sequences are embraced within the scope of the claim, and, consequently what method steps are supposed to achieve.

Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24,32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventors, at the time the application was filed, had possession of the claimed invention. The newly submitted claims introduce new matter because, first, they recite step of "selecting variant protein with altered immuniogenicity" (claim 24, step f).There is no disclosure in the specification on the meaning and scope of the "selection" and there is no guidance on how to practice the claimed method with such method step.

Further, there is no disclosure of synthesizing of variant proteins having more than one immunogenic sequence (claim 24, step b.ii).

4. Claims 24,32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The newly submitted claim 24 introduces new matter because it recites "sequences that bind to T cell epitopes". The specification as filed addresses T cell epitopes themselves as immunogenic sequences. There is no disclosure in the specification on the meaning and scope of the "sequences that bind to T cell epitopes" and there is no guidance on how to practice the claimed method with such method step.

5. Claims 24,32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to method of screening for altered immunogenicity of a target protein. This rejection addresses an embodiment wherein the resulting variant protein have same biological function but altered immunogenicity (unlike embodiments that would yield unrelated protein structures - as was addressed in rejections under 35 U.S.C. 112, second paragraph, above.

There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions on a real protein synthesized following its *in silico* design. The only mention of "immunogenicity filter" is so vague that it is not clear whether applicant was in possession of any algorithm or scoring function that would result in a design of a protein with altered immunogenicity.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must

describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that applicants generated any compound which, after computer generation, and application of "computational immunogenicity filters" had immunogenicity different from that of parent molecule. Similarly to *In re Wilde*r, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denie*d, 469 U.S. 1209 (1985) the specification did "little more than outline] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."

None of sufficient physical and/or chemical properties were found in the specification. In regard to functional characteristics specification correctly states that a sequence can be optimized using computational methods and that numerous known computerized algorithms predict binding of peptides to MHC molecules. Examiner does not dispute whether applicants were in possession of a method of determining binding to MHC molecules, however at issue is whether applicant was in possession of method of modulating immunogenicity. Discrepancy between predicted data on MHC binding and immunogenicity is well known. Thus, Meister et al. (i.e one of the methods used in the instant method) discusses that not all peptides predicted to bind to MHC peptides can be expected to stimulate immune response, both *in vivo* and *in vitro*. For example, only about one third (!) of peptides having motif corresponding to a given MHC allele have been found to interact with that MHC molecule. In some cases peptides which bind MHC molecules are immunodominant. See p. 598, second paragraph, and p. 582, second paragraph. Buus et al teaches that "there are still many examples of erroneous prediction of binding at the individual

peptide level; furthermore, interaction at one subsite may affect interactions at other subsites" (see paragraph bridging pages 211-212).

Section 112, first paragraph, requires the patentee to "show that an invention is complete by disclosure of substantially detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the invention. Even if the inventors were reasonably certain that immunogenicity of target protein can be modified using claimed computational methods, there is no showing in the patent that they knew that to be a fact. There is no showing of a single embodiment demonstrating modified immunogenicity. The reader can certainly appreciate the goal but establishing goals does not make a patent. As was mentioned in the rejection, the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993).

7. Claims 24,32 are rejected under 35 U.S.C. 112, first paragraph, as not being enabled.

First, in view of the concerns about ambiguity of the claims language expressed in the rejections under 35 U.S.C. 112, second paragraph, it is not clear how to make the invention as claimed.

There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions wherein a structure of a protein comprising a sequence binding to T cell epitopes is subjected to

in silico to computational modeling, then (or prior to) one or several immunogenic sequences (which may be any sequence) is replaced with a sequence capable of binding to T cell epitopes (which, again, can be any sequence). Note that any sequence of more than five amino acid residues is considered "immunogenic" in art. Further, as specificity of binding to T cell epitopes is not defined, any sequence is considered to be capable of binding to a T cell epitope, at least to some extent. Then, the claims read on remodeling protein structure and replacing one unspecified moiety with another unspecified moiety.

Second, It is not clear how to use the invention as claimed. The method produces proteins that have both altered core structure (claim 20, steps a-c), more than one of said altered core structure (claim 20, step d, "at least one" language), and added other moieties (claim 20, step d, "comprising" language). The latter can be from addition of several residues (p. 36, bottom) to addition of other large proteins which, obviously, will result in a protein having different functions and immunogenicity. In regard to alteration of the core structure, it, too, will be expected to change the functions of the target protein. This is because the peptide's structure is determined by the interplay of the hydrophobic/hydrophilic, stearic and electrostatic forces among the linked amino acid residues and It is not possible to predict the effect of replacing a single amino acid residue in a peptide's structure or bioactivity. Therefore, if replacing one or more residues in a peptide unpredictably alters its structure, this replacement also may alter bioactivity unpredictably.

In addition, the method as claimed encompasses proteins that are oligomers having plurality of altered core structure moieties (claim 20, step d, "at least one" language). It is not clear how to use such products.

Therefore, insufficient guidance exist in the specification to enable a person of skill in the art to practice the invention without the need for undue experimentation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Conclusion.

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

7/9/04

mlb

MICHAEL BORIN, PH.D
PRIMARY EXAMINER